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REVIEW ARTICLE

The effect of antidiabetic medications on non-alcoholic fatty liver disease (NAFLD)

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the metabolic syndrome and is prevalent in more than 50% of patients with type II diabetes. At present, there is no approved therapy for NASH. Until now, the only proven effective interventions in improving biochemical and histological features of NASH, including fibrosis, are weight loss and physical activity even without weight loss. Because of the common epidemiological and pathophysiological features between NAFLD and T2DM, many antidiabetics drugs have been tested in patients with NAFLD over the years. Among these, pioglitazone and liraglutide seem to improve some histological features of NASH but have no clear effect on fibrosis. Metformin has been largely studied in the past years without convincing evidence of improving NAFLD. Data on other compounds such as DDP-4 and SGLT-2 inhibitors are limited. The rational and results of such studies are discussed in the present review.

Keywords Steatohepatitis · Metformin · Liraglutide · Pioglitazone · HCC

Introduction

The term non-alcoholic fatty liver disease (NAFLD) includes a broad spectrum of liver diseases ranging from steatosis (NAFL) to non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis. The diagnosis of NAFLD relies on imaging [1] and histology, which enables the distinction to be made between simple fatty liver and NASH, where lobular inflammation and ballooning degeneration are also present [2, 3]. This distinction is not merely a didactic classification but predicts different outcomes: notably NAFL, due to its slower progression, is considered to have a benign course, whereas NASH is strongly associated with the risk of developing liver fibrosis, involving cirrhosis and its complications [4–6]. Moreover, in patients with NAFLD, the severity of fibrosis is the strongest predictor of liver-related outcomes [7, 8].

NAFLD is at present the most common liver disorder in Western countries, affecting about 25% of the population worldwide [9–11]; its prevalence ranges from 6 to 35% depending on different population groups, age, and diagnostic techniques; furthermore, NAFLD is the second cause of liver transplantation in the USA and is projected to become the leading indication for liver transplantation over the next decade [12].

This epidemic coincides with the rapidly increasing prevalence of obesity, type 2 diabetes (T2DM), and the metabolic syndrome (MS) in Western countries, with NAFLD being considered the hepatic manifestation of the latter [13]. MS is a cluster of different components sharing insulin resistance as the common pathophysiological feature [14]. Several studies demonstrated that MS is an independent predictor of development of NAFLD and NASH and its individual histological features, including fibrosis [15–20]; notably, the more components of MS affecting a patient, the more likely it is that NAFLD will develop [21]. However, NAFLD per se is also associated with a higher incidence of MS. [22]

Although strong evidence supports the link between NAFLD and metabolic syndrome, in some cases fatty liver can develop independently from MS, particularly in the presence of genetic variants of PNPLA 3 [23].

On this basis, many studies have focused on the relationship between NAFLD and diabetes, supporting with growing evidence a bidirectional causative link between them and identifying insulin resistance as the key factor of this connection [24, 25].

At present, there is no approved therapy for NASH. Until now, the only demonstrably effective interventions for

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improving biochemical and histological features of NASH, including fibrosis, are weight loss [26–28] and physical activity, the latter even without weight loss [29–31]. Because of the common epidemiological and pathophysiological features between NAFLD and T2DM, many antidiabetic drugs have been tested in patients with NAFLD over the years. The rationale for and results of these studies are discussed in the present review.

Metformin

Metformin is an insulin sensitizer which has a multiorgan effect resulting in a decrease in plasma glucose and free fatty acids (FFA); in particular, it reduces hepatic glucose production through suppression of gluconeogenesis and increased oxidation of fatty acids, inhibits lipolysis and subsequent FFA release from the adipose tissue, enhances glucose uptake and storage from the muscle, and reduces intestinal glucose absorption [32]. It is the preferred initial pharmacologic agent for the treatment of T2DM according to American and European guidelines [33, 34].

In a pilot study run in 2001 that included 20 non-diabetic patients, a 4-month course of metformin was associated with an improvement in serum aminotransferase levels, insulin sensitivity, and liver volume detected with ultrasound (US) in patients with NAFLD. The study included patients with fatty liver and increased ALT [35]. This study, as others which followed using larger numbers of patients, longer treatment, and histological outcomes failed to show any superiority of metformin over diet interventions and lifestyle changes [36–39].

A positive effect on transaminases was observed in a larger study with 110 non-diabetic NAFLD patients receiving nutritional counseling at baseline. Metformin was compared to vitamin E and dietetic intervention alone: aminotransferase levels improved in all groups, in association with weight loss, but the effects in the metformin group were more pronounced [40]. A subgroup of 17 metformin-treated patients with a histological diagnosis of NASH at baseline (the majority of whom did not meet the primary outcome of normalization of ALT levels after 1-year treatment with metformin) underwent a post-treatment biopsy which showed evidence of significant histological improvement in terms of steatosis, necroinflammation, and fibrosis.

Furthermore, metformin was studied in combination with rosiglitazone in a randomized clinical trial (RCT) involving 137 patients with biopsy-proven NASH (Table 1). Among the 108 subjects who completed the trial 18 were diabetic. Subjects were divided into three groups receiving, respectively, rosiglitazone and metformin, rosiglitazone and losartan, or rosiglitazone alone for 48 weeks. The primary outcome was improvement in steatosis, hepatocellular inflammation, or fibrosis; no significant difference was found between the three treatment groups even if the within-group comparison showed significant histological improvement of each component of NASH within all treatment arms [48].

Failure of metformin to significantly improve histological features in NASH was also confirmed in children and adolescents. The TONIC trial enrolled 173 non-diabetic patients aged 8–17 years old with biopsy-proven NAFLD and persistent increase in ALT. Patients were randomized to a 96-week course of metformin versus vitamin E versus placebo, and the primary outcome was ALT decrease, while histological improvement/NASH resolution was the secondary outcome. Neither vitamin E nor metformin was superior to placebo in achieving the primary outcome, whereas the resolution of NASH was significantly greater in the vitamin E group; metformin, apart from an isolated case of improvement in ballooning degeneration, did not significantly resolve NASH [50].

Interestingly, although there is no benefit to using metformin to treat NAFLD, metformin seems to be effective for NAFLD-related complications: dose-dependent reduction in hepatocellular carcinoma (HCC) was demonstrated in a large cohort of diabetic Taiwanese patients [51, 52] with a 7% reduction in the risk of HCC per year of metformin use. Furthermore, from a cardiovascular point of view, metformin is known to reduce cardiovascular complications related to diabetes [53] and therefore may contribute to reducing such complications among NAFLD patients who are more prone to develop coronary, cerebrovascular, and peripheral vascular disease independently of multiple CVD risk factors [54].

Peroxisome proliferator-activated receptor agonists

Thiazolidinediones are peroxisome proliferator-activated receptor γ (PPAR-γ) agonists and act as insulin sensitizers on the muscle, adipose tissue, and liver. PPAR are a family of nuclear transcription factors divided into different subtypes (PPAR α, γ, and β/δ) which have a large variety of effects on energy homeostasis and metabolism regulation. Compared to metformin, thiazolidinediones act more effectively on peripheral tissues (adipose tissue, muscle) than on the liver due to the specific distribution of their target receptors [55].

Rosiglitazone and pioglitazone have been extensively studied in NAFLD patients; however, rosiglitazone was withdrawn from the European market in 2010 because of a high risk of myocardial infarction [56]. Regarding rosiglitazone, RCTs demonstrated a biochemical improvement in liver enzymes and glycemic control both in diabetic and non-diabetic patients with NAFLD, whereas evidence of histological improvement is less clear: results derived from different

Table 1 Randomized controlled trials of antidiabetic medications in patients with biopsy-proven non-alcoholic steatohepatitis (NASH) that included more than 40 patients and used histology as the primary outcome

Author, year	Number of patients	T2DM	Intervention	Duration	Primary outcome	Result
Belfort, 2006 [41]	55	IGT/diabetics	Pioglitazone 45 mg vs placebo (1:1)	6 months	Improvement in histology, aminotransferase and metabolic parameters	Improvement in all main histological features except fibrosis
Aithal, 2008 [42]	74	Non-diabetics	Pioglitazone 30 mg vs placebo (1:1)	12 months	Reduction in hepatocyte injury and fibrosis score on histology	Significant reduction in steatosis, hepatocellular injury (ballooning, apoptosis, MD bodies) and fibrosis in pioglitazone group
Sanyal, 2010 [43]	247	Non-diabetics	Pioglitazone 30 mg vs vitamin E 800 IU vs. placebo (1:1:1)	96 weeks	Improvement in hepatocellular ballooning, no increase in fibrosis score, decrease of NAS score	Met the primary endopoint only in the vitamin E group
Cusi, 2016 [44]	101	Prediabetics and diabetics	Pioglitazone 45 mg vs. placebo (1:1)	18 months	Reduction of NAS score in 2 histological categories and no worsening of fibrosis	Met the primary endpoint with significant resolution of NASH
Idilman, 2008 [45]	74	Diabetics and non diabetics	Diet + exercise vs diet + exercise + insulinsensitizer (1:2)	48 weeks	Improvement in metabolic, biochemical and histological abnormalities	Met the primary endopoint
Ratziu, 2008 [46]	63	Diabetics and non- diabetics	Rosiglitazone 8 mg vs placebo (1:1)	1 year	Reduction/disappearance of steatosis	Significant reduction/disappearance of steatosis in rosiglitazone group
Ratziu, 2010 [47]	44	Diabetics and non- diabetics	Rosiglitazone 8 mg (extension phase of Ratziu 2008)	2 years	Reduction/disappearance of steatosis	Significant reduction/disappearance of steatosis only in patients treated with placebo in Ratziu 2008
Torres, 2011 [48]	137	Diabetics and non-diabetics	Rosiglitazone 8 mg vs rosiglitazone 8 mg + metformin 1 g vs rosiglitazone 8 mg + losartan 50 mg (1:1:1)	48 weeks	Improvement in steatosis, hepatocellular inflammation and fibrosis	No significant difference between groups
Armstrong, 2016 [49]	52	Diabetics and non-diabetics	Liraglutide 1.8 mg vs placebo (1:1)	48 weeks	Resolution of NASH without worsening of fibrosis	Primary outcome met in both diabetics and non-diabetics

T2DM type 2 diabetes mellitus, *IGT* impaired glucose tolerance, *MD* Mallory-Denk, *NAS* non-alcoholic fatty liver disease activity score

studies are controversial regarding the effect on steatosis, ballooning, and fibrosis [45, 46, 57, 58].

In a single-arm, open-label trial involving 22 overweight/obese patients with biopsy-proven NASH, 15 of them with impaired glucose metabolism, a 48-week course of rosiglitazone significantly improved the mean global necroinflammatory score, steatosis, hepatocellular ballooning, and fibrosis. [57] Different results were obtained from other two single-center trials. In a cohort of 74 patients with biopsy-proven NASH, 48-week treatment with rosiglitazone combined with diet and physical activity, compared to diet and exercise alone, was shown to significantly ameliorate NAS, steatosis, and ballooning, but no effect was detected on fibrosis [45]. Another study involved 64 patients with impaired glucose metabolism and biopsy-proven NAFLD who were randomly assigned to receive metformin or rosiglitazone or metformin plus rosiglitazone for 12 months. A control liver biopsy at the end of treatment was performed in 35 patients: NAS improvement was shown only in the groups receiving rosiglitazone, but still no significant effect on fibrosis was noted [58].

Moreover, in the FLIRT trial, 63 patients with biopsy-proven NASH and increased ALT, of whom 20 were diabetic, were randomized to receive either rosiglitazone or placebo for 1 year. The rosiglitazone group met the primary outcome of significant improvement/resolution of steatosis, whereas no

significant change was detected in any other histological lesions [46]. Subsequently, 44 out of the original 63 patients participated in the extension phase of this study (FLIRT 2) and were treated with rosiglitazone for two additional years. Interestingly, after this further treatment, significant improvement in steatosis was seen only in patients treated with placebo during the FLIRT, whereas patients who already received rosiglitazone during the FLIRT showed no additional benefit with the longer duration of treatment [47]. Combination treatment with metformin does not confer additional benefits apart from a partial mitigation of weight gain due to rosiglitazone [48].

Pioglitazone was also widely evaluated in clinical trials. A prospective pilot study run in 2004 involved 18 non-diabetic patients with biopsy-proven NASH and tested hepatic histological improvement as the primary outcome after a 48-week course of pioglitazone: the results showed significant improvement in histology regarding all major features of NASH (steatosis, parenchymal inflammation, cellular injury, and Mallory bodies) including fibrosis, despite a significant increase in body weight [59]. Follow-up after 48 weeks following the end of treatment revealed a significant recurrence of NASH in those who had previously recovered with a serum transaminase and histology similar to the baseline [60], suggesting the need for lifelong therapy. Interestingly, there was no worsening of fibrosis in these patients.

Promising evidence of the efficacy of pioglitazone among NAFLD diabetic patients has been demonstrated in a RCT of pioglitazone versus placebo involving 55 subjects, which showed a significant histological improvement of steatosis, inflammation and ballooning, and reduction in liver fat content (assessed by magnetic resonance spectroscopy) after treatment [41]. In this study, no effect of pioglitazone on liver fibrosis was shown.

A subsequent double-blind RCT conducted in 2008 that included 74 non-diabetic patients with NAFLD confirmed the beneficial effects of pioglitazone on liver histology. The primary outcome was the reduction in hepatocyte injury (namely cellular ballooning, apoptosis, and necrosis) and fibrosis score. Pioglitazone was tested versus placebo and showed a significant improvement not only in steatosis but also in hepatocyte injury, lobular inflammation, Mallory bodies, and fibrosis [42].

Compared to these studies, contrasting results have been collected from a big multicenter phase III RCT (the PIVENS trial) which involved 247 non-diabetic patients with biopsy-proven NASH and compared vitamin E versus pioglitazone versus placebo after a 96-week treatment period. In this trial, only vitamin E met the prespecified significance level of the primary outcome (i.e., improvement in histological findings, which included an improvement in hepatocellular ballooning), although both active treatment groups had a significant reduction in steatosis, lobular inflammation, and NAS (NAFLD activity score). This result was explained by the authors as the lack of hepatocellular ballooning in a more consistent percentage of subjects within the pioglitazone group on initial biopsies as assessed after central review. In fact, when subjects who initially did not have hepatocellular ballooning were excluded from the analyses, both active drug groups were associated with a significant improvement in histological findings. Neither vitamin E nor pioglitazone significantly improved the fibrosis score in this study [43].

More recently, Cusi et al. ran a similar RCT involving 101 prediabetic and diabetic patients with biopsy-proven NASH who were randomized to receive pioglitazone or placebo for 18 months. The pioglitazone group, compared to placebo, showed a significant improvement of NAS and no worsening of fibrosis (primary outcome). Moreover, in the pioglitazone group, there was a significant resolution of NASH, significant improvement in all the single main features of NASH (steatosis, inflammation, and ballooning necrosis), and significant reduction in the fibrosis score. Extending treatment with pioglitazone for a further 18 months yielded no additional benefit [44].

A meta-analysis of thiazolidinediones corroborated the beneficial effects of pioglitazone on liver fibrosis. It included 8 RCTs (5 evaluating pioglitazone and 3 evaluating rosiglitazone) enrolling 516 patients with biopsy-proven NASH for a duration of 6 to 24 months. Thiazolidinedione therapy was associated with improving advanced fibrosis (OR 3.15, 95% CI, 1.25–7.93), fibrosis of any stage (OR 1.66, 95% CI, 1.12–2.47), and NASH resolution (OR 3.22, 95% CI, 2.17–4.79). Similar results were obtained restricting analyses to RCTs enrolling non-diabetic patients. Beneficial effects were accounted for by pioglitazone use, whereas rosiglitazone use did not reach statistical significance for any histological outcome [61].

It is important to underscore the fact that pioglitazone is associated with potentially serious adverse events such as fluid retention, weight gain, and increased risk of congestive heart failure, albeit in the absence of increased cardiovascular mortality [62, 63]. Notably, weight gain seems to persist even after discontinuation of the drug [60].

Regarding other PPAR agonists, research is currently focusing on the development of new molecules for the treatment of NAFLD. Saroglitazar, a dual PPAR α/γ agonist currently used in India for treatment of diabetic dyslipidemia has shown promising effects in experimental models of NASH [64] and seems also to be effective in humans, reducing serum aminotransferase levels and liver size assessed by ultrasound in NASH patients after a 24-week course [65]; a small-phase IIa single-arm clinical trial (PRESS VIII) using saroglitazar in biopsy-proven NASH patients has finished recruitment and its results are awaited. In contrast to pioglitazone, saroglitazar does not seem to correlate with weight gain and peripheral edema [66].

Other than saroglitazar, elafibranor, a PPAR α/δ agonist, was tested in a 1-year phase II RCT involving 274 subjects with biopsy-proven NASH, 107 of whom were diabetic: using a modified post hoc primary endpoint, elafibranor resolved NASH in a significant percentage of patients, without worsening of fibrosis, and ameliorated the hepatic and metabolic profile [67]. In this large study, no cardiovascular events or deaths in the elafibranor arm were reported. Currently, a phase III RCT evaluating histological improvement, all-cause mortality and liver-related outcomes in patients with NASH and fibrosis is ongoing. (ClinicalTrials.gov Identifier: NCT02704403).

Lobeglitazone, a PPARα/γ agonist licensed in Korea for treatment of T2DM, has recently been studied in a pilot trial recruiting diabetic NASH patients diagnosed by CAP values on Fibroscan; this drug was shown to reduce CAP values independently of a glucose-lowering effect and to improve lipid, glycemic, and hepatic serum parameters [68].

Glucagon-like peptide 1 receptor (GLP-1 R) agonists

This class of drugs (which includes liraglutide, exenatide, lixisenatide, and dulaglutide) acts on the pancreas, brain, and adipose tissue in a way similar to physiological GLP 1 and exerts its antidiabetic effect through controlling food intake, energy absorption, and glucose-dependent insulin secretion [69]. They are considered a second-line treatment for T2DM [33]. Apart from their glucose-lowering effect, they have further positive consequences such as cardio-protective effects [70, 71] and an induction of weight loss which is very beneficial in patients with NAFLD [72].

In a meta-analysis including 4442 patients, liraglutide improved serum transaminases in diabetic patients; this effect is thought to be mediated by its action on weight loss and improved glycemic control [73].

Moreover, apart from the presence or absence of NAFLD, liraglutide reduced liver fat content as assessed by MRI spectroscopy in patients with uncontrolled T2DM thanks to its weight-lowering effect, whereas insulin glargine, despite its effective control of glycemic status, produced no improvement in weight loss and liver fat content [74]. However, these results have been in contrast to those obtained by Tang who compared the effect of a 12-week course of insulin glargine versus liraglutide among 35 patients with T2DM inadequately controlled on metformin monotherapy or in combination with other oral antidiabetic drugs. Despite similar glycemic control, the insulin group showed significant reduction in liver fat burden assessed radiologically (mean MRI-PDFF, liver volume, total liver fat index), whereas no significant change was detected in the liraglutide group [75]. In agreement with the results of Tang, no changes in liver fat content and surrogate biomarkers of fibrosis were shown in a RCT comparing the effect of a 12-week course with liraglutide versus sitagliptin or placebo among 52 overweight diabetic patients on metformin or sulphanylurea. Results did not change when restricting the analysis to patients with NAFLD at baseline (15 patients in the liraglutide group, 16 in the sitagliptin group, and 15 in the placebo group) [76].

Histological effects of liraglutide have recently been studied in a pilot phase II multicenter RCT involving 52 patients with biopsy-proven NASH, 17 of whom had T2DM; liraglutide met the primary endpoint of NASH resolution without worsening of fibrosis both in diabetic and non-diabetic patients. These results were attributed in part to a cumulative effect on weight loss and glycemic control [49]. In this trial, a subgroup of patients was assessed for organ-specific insulin sensitivity, hepatic lipid handling, and adipose dysfunction: the results showed that liraglutide improved hepatic and adipose insulin sensitivity and reduced the hepatic de novo lipogenesis [77], a key component of the hepatic fat accumulation in NASH.

Evidence of a hepatoprotective effect also exists for exenatide: this drug has been evaluated in several randomized clinical studies involving T2DM and obese patients and was shown to reduce liver enzymes, hepatic fat content, hepatic triglyceride content, and epicardial fat [78–80]. Similarly to other GLP-1R agonists, results were influenced by the simultaneous weight loss observed in these studies. Histological efficacy of exenatide was investigated in eight diabetic patients with biopsy-proven NAFLD but, although some improvement in isolated histologic features and fibrosis was demonstrated, there was no statistical significance, most likely due to the small sample size [81].

The impact of lixisenatide and dulaglutide on NAFLD is not well known till now as few studies have been completed [82, 83].

Another GLP-1 agonist, semaglutide, is in development for the treatment of T2DM. An ongoing phase IIb RCT, currently recruiting patients, aims to evaluate the safety and efficacy of this drug in NASH with a primary outcome consisting in NASH resolution without worsening of fibrosis. The trial, which has a duration of 72 weeks, is due to finish in July 2019 (ClinicalTrials.gov Identifier: NCT02970942).

The vast majority of these studies highlighted frequent gastrointestinal side effects from GPL-1 RA; however, these usually subside after the initial phase of dose escalation (usually 6 weeks).

Dipeptidyl dipeptidase-4 inhibitors

These drugs, consisting primarily of sitagliptin, vildagliptin, linagliptin, saxagliptin, and alogliptin, enhance the effects of incretins by inhibiting dipeptidyl dipeptidase 4 (DPP-4), the

enzyme responsible for their degradation. Incretins are a group of metabolic hormones released from the bowel in response to a meal. The main molecules of this group, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), exert a common glucoregolatory effect stimulating insulin biosynthesis, β-cell proliferation, and glucose-dependent insulin secretion from the pancreas: furthermore, they exert different multiorgan effects. In particular, GLP-1 acts on the stomach slowing gastric emptying and, indirectly, enhances glucose uptake from the muscle and adipose tissue. Because native incretins have a very short half-life, degradation resistant GLP-1R agonist and inhibitors of DDP-4 have been developed as antidiabetic medications [69].

DPP-4 inhibitors are neutral on body weight and on the cardiovascular system according to major cardiovascular event rates, even if the rate of hospitalization due to heart failure was increased for saxagliptin [84–86].

In animal models of NASH, DPP-4 inhibitors showed promising results, preventing the development of steatohepatitis by affecting both inflammatory and fibrosis pathways; this effect seems to be due to different mechanisms, including reduced expression of proinflammatory mediators such as TNFα, IL-6, and p-NFkB, attenuation of endoplasmic reticulum stress, reduction in hepatocyte apoptosis, decreased accumulation of fibronectin and alpha-smooth muscle actin (α-SMA), and reduction in plasminogen activator inhibitor 1 (PAI-1) expression [87, 88]. Nevertheless, in humans, the efficacy of DPP-4 inhibitors on NAFLD was more difficult to prove and results yielded to date are conflicting.

Although a small observational pilot study on 15 diabetic patients with biopsy-proven NAFLD demonstrated biochemical and histological improvement after a 1-year course of sitagliptin [89] further RCTs failed to demonstrate any beneficial effect of sitagliptin on NAFLD in diabetic patients. Limitations of these studies are the small number of patients involved, the relatively short duration of intervention (6 months), and the lack of evaluated histological outcomes [90, 91].

Furthermore, in a 24-week RCT involving 52 overweight patients with T2DM, sitagliptin was compared with liraglutide and placebo according to the study endpoints of evaluation of hepatic fat content and hepatic fibrosis: no difference in hepatic fat content measured with H-MRS and surrogate indicators of liver fibrosis was shown between the three groups [76].

On the other hand, a Japanese single-center, open-label trial compared sitagliptin at suboptimal dosage with glimepiride in a cohort of 20 diabetic patients with ultrasound evidence of fatty liver: after 24 weeks of treatment, in the sitagliptin group but not in the glimepiride group, there was a significant reduction in intrahepatic lipid content and total body fat mass on H-MRS and DEXA despite a similar decrease in HbA1c [92].

There are even fewer studies supporting the effect of other types of DPP-4 in NAFLD: in a double-blind RCT involving 44 patients with well-controlled T2DM vildagliptin was proven to reduce liver trygliceride content assessed by MRI along with achieving a significant improvement in serum transaminase and fasting plasma glucose after a 6-month course; [93] for alogliptin evidence of any effects in NAFLD is poor [94].

Further data supporting the efficacy of this class of drugs are awaited from two similar ongoing phase III clinical trials: NCT02147925 aims to compare the change of intrahepatic lipids (IHL) in type 2 diabetic patients with non-alcoholic fatty-liver disease after a 26-week treatment of liraglutide, sitagliptin, or insulin glargine per day combined with metformin, while NCT02365233 will assess a similar outcome comparing pioglitazone to DPP-4 inhibitors (sitagliptin or saxagliptin) to insulin glargine.

Sodium-glucose co-transporters (SGLT2) inhibitors

This class of antidiabetic drugs lowers plasma glucose by inhibiting glucose reabsorption in the renal proximal tubule. Their mechanism of action is independent from insulin secretion or action and is not affected by pancreatic β-cell function, making them a suitable potential therapy at any stage of T2DM progression [95].

Canaglifozin, dapaglifozin, and empaglifozin are the active substances approved in Europe and the USA as second-line treatment in association with metformin as well as third-line treatment [33]. Other molecules, namely ipraglifozin, luseoglifozin, and tofoglifozin, are approved only in Japan, while molecules such as ertuglifozin and sotaglifozin are in clinical development.

Apart from their well-recognized efficacy in improving the glycemic profile in diabetic patients, SGLT2 inhibitors have shown numerous beneficial effects separate from glycemic control, which makes them a potentially useful therapy in the context of NAFLD and its complications. In particular, they can induce weight loss by decreasing body fat mass and exert cardiorenal protection by lowering blood pressure, arterial stiffness, and renal hyperfiltration [96]. Notably, long-term effects of empaglifozin on renal and cardiovascular outcomes were assessed with the EMPA REG OUTCOME trial which demonstrated a reduction in the risk of death from cardiovascular disease (HR 0.62, 95% CI, 0.49–0.77), hospitalization for heart failure (HR 0.65, 95% CI, 0.50–0.85), and death from any cause (HR 0.68, 95% CI, 0.57–0.82) [97], as well as slower progression of kidney disease (HR 0.61, 95% CI, 0.53 to 0.70) and lower rates of clinically relevant renal events than placebo (HR 0.54, 95% CI, 0.40–0.75). [98]

Based on the above evidence, SGLT2 inhibitors have been tested in numerous NAFLD animal models, showing promising results. In obese mice with diet-induced NAFLD, remoglifozin reduced plasma aminotransferase levels, liver

weight, and hepatic triglyceride content [99]. Empaglifozin was studied alone and in combination with linagliptin in a novel mouse model of NASH and diabetes showing antisteatotic and anti-inflammatory effects in both cases, while an antifibrotic effect was demonstrated only in combination with linagliptin [100]. Beneficial effects on liver steatosis in animal models are also observed with regard to other SGLT2 inhibitors such as luseoglifozin and ipraglifozin [101, 102].

Human studies assessing the efficacy of SGLT2 inhibitors for NAFLD are still scarce: there is some evidence that canaglifozin and dapaglifozin may lower serum aminotransferase in diabetic patients [103, 104] but data on histological outcomes are lacking. Their side effects include increased risk of genital mycotic infections and urinary tract infections, diabetic ketoacidosis, and bone fractures [96]. Due to their mechanism of action, which is independent from β cell function, SGLT2 inhibitors do not cause hypoglycemia. In February 2017, the European Medicines Agency (EMA) issued a warning concerning increased risk of lower limb amputation (especially toes) related to SGLT2 inhibitor therapy, although this risk was demonstrated to be significant only for canaglifozin [105].

α-glucosidase inhibitors

Acarbose and miglitol inhibit the intestinal enzyme α-glucosidase, which is responsible for the breakdown of complex carbohydrates into small monosaccharides and thereby slows intestinal carbohydrate digestion and absorption. Due to their only modest antidiabetic efficacy, the frequency of administration, and their side effects, they are not often used in clinical practice [33].

Despite some scientific interest concerning the use of acarbose for the treatment of NAFLD [106], data are scarce on the effect of this class of drugs in NAFLD animal models [107, 108] and are non-existent in humans. Acarbose was occasionally associated with a mild symptomless increase in aminotransferase levels and even one case of acute hepatotoxicity [109], which was however identified as an idiosyncratic reaction. Despite this, acarbose has been demonstrated to be safe in patients with cirrhosis [110] and to reduce cardiovascular events and hypertension among patients with impaired glucose tolerance [111].

Intensive insulin therapy

Although insulin resistance is a major contributor to the development of NAFLD in most cases [40], insulin therapy has not been proved to resolve or improve NAFLD. On the contrary, insulin therapy has been associated with weight gain and increased risk of cardiovascular events [112, 113], which are common risk factors in patients diagnosed with NAFLD.

Conclusions

Despite the huge progress made in the understanding of the natural history and the pathophysiology of NAFLD [114], effective therapeutic options are still lacking. Among the existing antidiabetic drugs, the evidence of potential efficacy is strongest for pioglitazone; there are, however, important potential side effects, notably peripheral edema resulting in weight gain, that need to be considered. Liraglutide is also promising; however, further data are required. Other

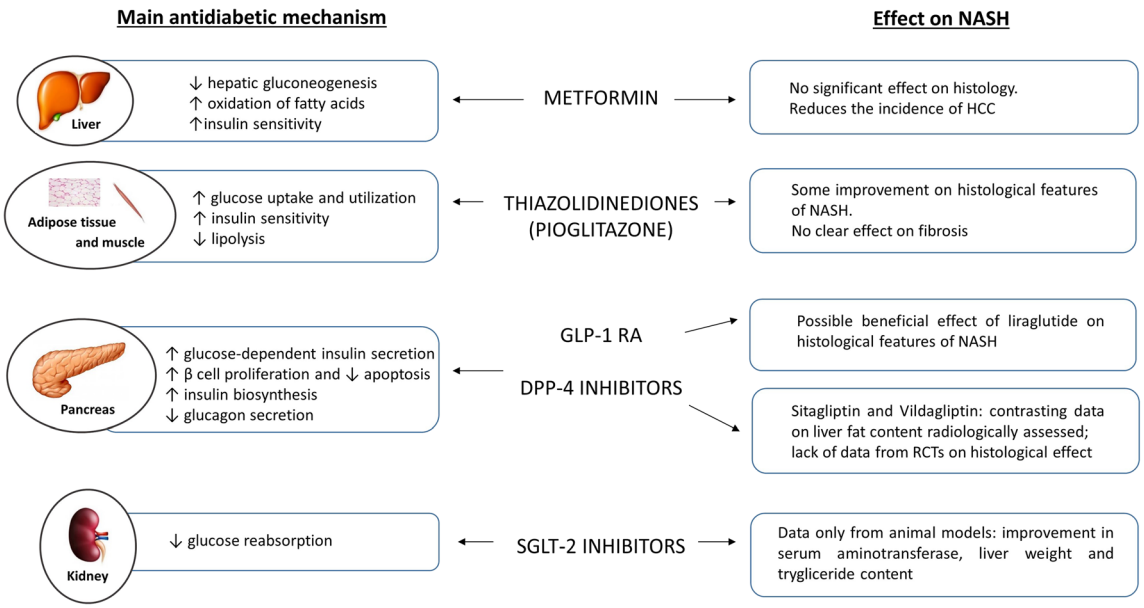

Fig. 1 Main antidiabetic mechanism of action and effects on fatty liver according to different antidiabetic drug classes

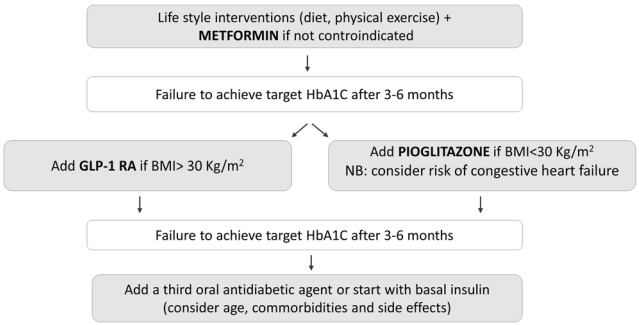

Fig. 2 Stepwise approach in the management of type II diabetes in patients with non-alcoholic fatty liver disease (NAFLD)

antidiabetic drugs such as DPP-4 inhibitors and SGLT2 inhibitors could also be a promising option and further studies with histological outcomes are awaited [115, 116]. The potential mechanism of action of these drugs on the liver is summarized in Fig. 1.

According to the available evidence, it would be clinically useful to follow a stepwise approach to antidiabetic treatment in patients with NAFLD. Metformin, as suggested by the international guidelines, should be the first-line treatment: patients with NAFLD can benefit from its positive impact on body weight (tendency to weight loss) and from a decrease in the risk of HCC, which seems to occur even in absence of cirrhosis in these patients [117]. Second-line treatment should be chosen according to the nutritional status of the patient (i.e., BMI): in obese patients (BMI > 30–35 kg/m^2), GLP-1 agonists could be a helpful option considering their positive effect on body weight and potential beneficial effect on histology, whereas in normal weight or overweight patients (BMI < 30 kg/m^2), use of pioglitazone can be justified even if it associated with weight increase. A potential treatment algorithm is shown in Fig. 2.

In the next few years, the scenario in the treatment of NAFLD is expected to change when currently conducted large phase IIb and III trials with histological outcomes publish their results (ClinicalTrials.gov Identifier: NCT02970942 and NCT02704403); semaglutide and elafibranor may be effective not only for steatosis and inflammation but also for fibrosis and thus be able to modify the strongest predictor of disease-specific mortality in patients with NAFLD.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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